On page 11, lines 16-26, please replace the test with the following paragraph:

A sixth method of determining whether a test composition is useful for alleviating a bone-related disorder compresses maintaining an artificial membrane (e.g. a liposome or a re-sealed erythrocyte) which comprises a biologically active MRR protein in the presence of the test composition and comparing i) an activity of the MRR protein of the artificial membrane maintained in the presence of the test composition and ii) the same activity of the MRR protein of an artificial membrane of the same type maintained in the absence of the test composition. A difference between i) the activity of the MRR protein of the artificial membrane maintained in the presence of the test composition and ii) the same activity of the MRR protein of artificial membrane of the same type maintained in the absence of the test composition is an indication that the test composition is useful for alleviating a bone-related disorder.

On page 14, lines 18-26, please replace the text with the following paragraphs:

Figure 3 is an image generated in a *in situ* hybridization experiment in which mRNA encoding MRR protein was detected in a whole mount of an 18.5-day murine embryo. MRR-encoding mRNA is indicated by dark shading. The presence of MRR-encoding mRNA is evident in, for example, vertebral and limb bone precursors in the embryo.

Figure 4, comprising Figures 4A, 4B, 4C, and 4D, is a quartet of images of 18.5-day murine embryonic limb bone precursor (Figures 4A and 4B) and vertebral disk bone precursor (Figures 4C and 4D). Figures 4A and 4C are images of the microscopic appearance of these tissues, and Figures 4B and 4D depict the presence of MRR protein, as assessed by fluorescent *in situ* hybridization using an antibody which binds specifically with MRR.

On page 16 lines 25-31, please replace the text with the following paragraph:

In yet another embodiment of the method of diagnosing a bone-related disorder in a human patient, the level of expression of an mrr gene in a tissue of the patient is determined and compared with the level of expression of the mrr gene in the same tissue of a human not afflicted with the bone-related disorder. A difference between the level of expression of the mrr gene in the tissue of the patient and the level of expression of the mrr gene in the same tissue of the human not afflicted with the bone-related disorder is an indication that the patient is afflicted with the bone-related disorder.

On page 26, line 22 to page 27, line 17, please replace the text with the following paragraphs:

In screening methods of the invention that involve determining the activity of an MRR protein, the activity may, for example, be selected from the group consisting of a proteolytic activity (e.g. ability of the carboxyl-terminal portion of MRR protein to cleave a peptide bond of a polypeptide), a pore-modulating activity (e.g. ability of MRR protein to activate or de-activate a transmembrane protein pore), an enzyme-modulating activity (e.g. ability of MRR protein to modify an enzyme in a manner that increases or decreases the enzyme's activity), and a gene transcription-modulating activity (e.g. ability of MRR protein to enhance or inhibit expression of a gene).

Interactions between MRR protein and test compositions can also be assessed using chimeric receptor proteins in which the amino-terminal extracellular domain, or parts thereof, the entire transmembrane domain or sub-regions, such as any of the seven transmembrane segments or any of the intracellular or extracellular loops and the carboxyl-terminal intracellular domain, or parts thereof, are be replaced by heterologous domains or sub-

regions. For example, a G-protein-binding region can be used that interacts with a different G-protein than that which is recognized by the native MRR protein. Accordingly, a different set of signal transduction components is available as an end-point assay for activation. Alternatively, the entire transmembrane portion or sub-regions (e.g. the transmembrane segments or intracellular or extracellular loops) can be replaced with the entire transmembrane portion or sub-regions specific to a host cell that is different from the host cell from which the amino-terminal extracellular domain and/or the G-protein-binding region are derived. This allows assays to be performed in other than the specific host cell from which the receptor is derived. Alternatively, the amino-terminal extracellular domain (or other ligand-binding regions, or both) can be replaced by a domain (or other binding region, or both) which binds a different ligand, thereby providing an assay for test compounds that interact with the heterologous amino-terminal extracellular domain (or region) but still cause signal transduction. Furthermore, activation can be detected using a reporter gene containing an easily detectable coding region operably linked to a transcriptional regulatory sequence that is part of the native signal transduction pathway.

On page 28, line 12-31, please replace the text with the following paragraph:

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, an MRR protein of the invention or a ligand thereof can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated polypeptides or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with MRR protein or a ligand thereof but which do not interfere with binding of MRR protein to its ligand can be derivatized to the wells of the plate,

and non-bound ligand or MRR protein of the invention trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the glutathione S-transferase (GST)-immobilized complexes, include immunodetection of complexes using antibodies reactive with MRR protein or a ligand thereof, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with MRR protein or a ligand thereof. It can be desirable to utilize a solubilizing agent such that the membrane-bound form of the polypeptide is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-octylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton X-100, Triton X-114, Thesit, Isotridecypoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl) dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl) dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate.

On page 32, line 23-33, please replace the text with the following paragraph:

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called DNA mismatch repair enzymes) in defined systems for detecting and mapping point mutations in cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) Carcinogenesis 15:1657-1662). According to one embodiment, a probe based on a selected sequence, e.g., a wild-type sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. See, e.g., U.S. Patent No. 5,459,039.

On page 34 line 21-29, please replace the text with the following paragraph:

Because, as described herein, MRR is a GPCR, MRR can also exhibit one or more properties which GPCRs commonly exhibit. For example, GPCRs are known to participate in transmembrane signaling systems. In such systems, the GPCR acts as an integral membrane transducer which couples binding of a ligand to the GPCR on the extracellular side of the membrane to modulation of the physiological activity of one or more proteins within the cell cytoplasm. Most GPCRs directly modulate one or more physiological activities of a G-protein which is capable of associating with the intracellular (i.e. carboxyl-terminal) portion of the GPCR. The corresponding G-protein, the GPCR, or both, also can exhibit one or more of the following activities:

On page 35, line to page 36, line 3, please replace the text with the following paragraphs:

Upon binding a ligand at its extracellular (i.e. amino-terminal) portion, MRR protein facilitates interconversions of one or more molecules (e.g. proteins, phosphorylated organic compounds, or both) involved in turnover and metabolism of phosphatidylinositol 4,5-bisphosphate (PIP_2). PIP_2 is a phospholipid which occurs in the cytosolic leaflet of the plasma membrane. For example, binding of a ligand to MRR can phospholipase C, which catalyzes hydrolysis of PIP_2 to yield 1,2-diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3). Once formed, IP_3 can diffuse to the endoplasmic reticulum surface where it can bind a calcium channel protein which specifically binds with IP_3. IP_3 binding can induce opening of the channel, allowing calcium ions to be released into the cytoplasm. IP_3 can also be phosphorylated by a specific kinase to form inositol 1,3,4,5-tetraphosphate (IP_4), a molecule which can cause

calcium entry into the cytoplasm from the extracellular medium. IP_3 and IP_4 can subsequently be hydrolyzed very rapidly to the inactive products inositol 1,4-biphosphate (IP_2) and inositol 1,3,4-triphosphate, respectively. These inactive products can be recycled by the cell to synthesize PIP_2. Hydrolysis of PIP_2 also yields DAG, which remains in the cell membrane where it can activate the enzyme protein kinase C. Protein kinase C is usually found soluble in the cytoplasm of the cell, but upon an increase in the intracellular calcium concentration, this enzyme can move to the plasma membrane where it can be activated by DAG. Activation of protein kinase C can result in various cellular responses, such as phosphorylation of glycogen synthase or phosphorylation of various transcription factors (e.g. NF-kB).

Upon binding a ligand at its extracellular (i.e. amino-terminal) portion, MRR protein can also participate is a cAMP signaling pathway. In such a cAMP signaling pathway, binding of a ligand to MRR leads to activation of adenylate cyclase, which catalyzes synthesis of cAMP. Newly synthesized cAMP can activate a cAMP-dependent protein kinase. This activated kinase can phosphorylate a voltage-gated potassium channel protein, or a protein associated with such a channel, inhibiting the ability of the potassium channel to open in the presence of an action potential. Inability of the potassium channel to open results in a decrease in the outward flow of potassium, which can reduce or inhibit polarization of the cytoplasmic membrane.

On page 38 lines 33-36, please replace the text with the following paragraph:

A nucleic acid fragment encoding a biologically active portion of a polypeptide of the invention can be prepared by isolating a portion of one of SEQ ID NOs: 2, 4, and 6,

expressing the encoded portion of the polypeptide protein (e.g., by recombinant expression *in vitro*), and assessing the activity of the encoded portion of the polypeptide.

On page 43, lines 5-20 please replace the text with the following paragraph:

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind with cellular mRNA and/or genomic DNA encoding a selected polypeptide of the invention to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds with DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind with receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind with cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

On page 45, lines 22-31, please replace the text with the following paragraph:

In other embodiments, the oligonucleotide can include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport

across the cell membrane (see, e.g., Letsinger et al. (1989) Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al. (1987) Proc. Natl. Acad. Sci. USA 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, e.g., PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, e.g., Krol et al. (1988) Bio/Techniques 6:958-976) or intercalating agents (see, e.g., Zon (1988) Pharm. Res. 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

On page 47 line 21 to page 48 line 9, please replace the text with the following paragraph:

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) Nucleic Acids Res. 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between

molecules. Id. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) CABIOS 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

On page 49, lines 1-13, please replace the text with the following paragraph:

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a polypeptide of the invention is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a polypeptide of the invention. Inhibition of ligand/receptor interaction can be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g. promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a polypeptide of the invention in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of receptors with ligands.

On page 54 lines 5-9, please replace the text with the following paragraph.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers et al. (1994) Biotechnology 12:899-903).

On page 55, line 15 to page 56, line 8, please replace the text with the following paragraphs:

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can

depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

On page 56, line 3 to page 57, line 8, please replace the text with the following paragraph:

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic (e.g., *E.coli*) or eukaryotic cells (e.g., insect cells (using baculovirus expression vectors), yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, supra. Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc;

Smith and Johnson (1988) Gene 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E.coli* expression vectors include pTrc (Amann et al., (1988) Gene 69:301-315) and pET 11d (Studier et al., Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident ? prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E.coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al. (1992) Nucleic Acids Res. 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

On page 58 lines 30-31, please replace the text with the following paragraph:

A host cell can be any prokaryotic (e.g., *E. coli*) or eukaryotic cell (e.g., insect cells, yeast, or mammalian cells).

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On page 68, line 18 to page 69, line 7, please replace the text with the following paragraph:

A preferred agent for detecting a polypeptide of the is an antibody capable of binding to the polypeptide, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vivo* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. In vitro techniques for detection of a polypeptide of the include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a polypeptide of the invention include introducing into a subject a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.